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(54) Title: APPARATUS AND METHOD FOR IMAGING DISEASED TISSUE USING INTEGRATED AUTOFLUORESCENCE

(57) Abstract

An apparatus and method for imaging diseases in tissue are presented. The apparatus employs a light source for producing excitation light to excite the tissue to generate autofluorescence light and for producing illumination light to generate reflected and back scattered light (remittance light) from the tissue. Optical sensors are used to receive the autofluorescence light and the remittance light to collect an autofluorescence light image and a remittance light image. A filter acts to integrate the autofluorescence image over a range of wavelengths in which the autofluorescence intensity for normal tissue is substantially different from the autofluorescence intensity for diseased tissue to establish an integrated autofluorescence image of the tissue. The remittance light image provides a background image to normalize the autofluorescence image to account for image non-uniformity due to changes in distance, angle and illumination intensity. A monitor displays the integrated autofluorescence image and the remittance light image to produce a normalized image in which diseased tissue is distinguishable from normal tissue. The optical sensor can be installed adjacent the end of an endoscope probe inserted into a body cavity. A method for imaging diseased tissue using an integrated fluorescence image and a normalizing remittance image is also disclosed.

APPARATUS AND METHOD FOR IMAGING DISEASED TISSUE
USING INTEGRATED AUTOFLUORESCENCE

FIELD OF THE INVENTION

5   This invention relates to an endoscope apparatus and
method for viewing tissue within the body that uses
autofluorescence of the tissue to detect and delineate
diseased tissue.

BACKGROUND OF THE INVENTION

10   Fluorescence endoscopy involves introducing
excitation light into the body and collecting the emitted
fluorescence light by means of a probe that is inserted
into the body to the location of interest. The probe
comprises a lens fitted onto a coherent bundle of glass
15   fibres which brings the fluorescent image out of the body
cavity. Alternatively, the probe can be a rigid
endoscope without fibre optics. The image brought out of
the body is captured by very sensitive photodetectors and
further processed in an attempt to delineate diseased
20   tissue on the basis that diseased tissue has a different
fluorescence intensity than normal tissue. This process
loses significant amounts of light due to the image
transfer through the optical fibres and a great deal of
effort in developing new fluorescence endoscope systems
25   is directed toward new ways of acquiring, enhancing and
analyzing the very faint fluorescence images to extract
as much information as possible.

       Other work has been done in this field that attempts
to exploit the different fluorescence spectra of diseased
30   and healthy tissue. United States Patents 5,131,398 to
Alfano, United States Patent 4,930,516 to Alfano, and
United States Patent 4,786,813 to Svanberg et al.
disclose various equipment and methods that acquire and

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process fluorescence images in an attempt to detect and
delineate diseased tissue.

At present, many fluorescence endoscopy systems rely
on drugs with strong fluorescence signals as well as very
5 sensitive detectors to detect the emitted fluorescence
signals. Applicant has developed equipment that employs
tissue autofluorescence alone, without drugs, to detect
diseased tissues such as early cancer and others. In
this approach, very faint fluorescence signals must be
10 measured at two or more specific wavelengths of emitted
fluorescence. To accomplish such a measurement, very
sensitive detectors, such as image intensified cameras
operating at the limit of their working range must be
used. This arrangement works well for detecting some
15 tumours, but care must be taken to correctly adjust the
autofluorescence signals to create appropriate images
with minimal noise in order to recognize the diseased
site under examination. Also, image intensified cameras
(or similar detectors) are very large, they employ high
20 voltage circuitry and they cannot be made to fit the end
of the endoscope. The fluorescence images must therefore
be brought out of tissue cavities through the coherent
optical fibers of the endoscope before processing of the
images and/or displaying them on a video monitor.

25   It has been suggested that the acquired fluorescence
image of endoscope systems would be of better quality if
it could be collected by a sensor at the end of the
endoscope probe inserted into the body. The outer
diameter of an endoscope probe must be small to allow
30 insertion into various body cavities thereby limiting the
size of the sensor that can be mounted at the distal end
of the apparatus. As previously stated, fluorescence
images are generally extremely faint and it is not
possible for these small image sensors to capture the
35 fluorescence images. Theoretically, increasing the

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excitation irradiance would increase the fluorescence
intensity, however, this may also result in unwanted
thermal damage or photobleaching of the tissue under
examination.

5   Prior art endoscopes have been developed that permit
the image sensor to be located at the tip of the
endoscope probe, however, in general, this endoscope
equipment is intended for collecting reflected light and
is not suitable for reliably capturing faint fluorescence
10   images.

SUMMARY OF THE INVENTION

The present invention seeks to provide an apparatus
and method that addresses the problems of the prior art
by providing a new system for acquiring fluorescence
15   images that uses integration of autofluorescence
intensity over a broad band of wavelengths to acquire a
well-defined autofluorescence image that is combined with
a remittance light image to create a merged image in
which diseased and normal tissue are readily
20   distinguishable. The remittance light image is used to
normalize the autofluorescence image to account for image
non-uniformity due to changes in distance, angle and
illumination intensity.

The present invention exploits applicant's discovery
25   that in vivo tissue autofluorescence of diseased tissue
is greatly reduced through a significant range of the
visible light spectrum (from approximately 500nm to
approximately 700nm). To exploit this natural
phenomenon, the present novel system was designed and
30   developed to use the integrated fluorescence over this
large spectral range (500 nm - 700 nm) and display the
fluorescence image along with a remittance light image
such that, to the observer, normal tissue appears in a

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different colour from diseased tissue. In the present
application, remittance light refers to reflected and
back scattered light. Fluorescence signal intensity is
dependent on such factors as the excitation light
5   intensity, the proximity of the excitation light source
to the tissue, and the angle of incidence of the
excitation light to the tissue. To normalize for these
factors, prior art systems have used two (or more)
different narrow wavelength bands of fluorescence, one of
10   which is used for normalization purposes. This requires
a precondition that the difference in the tissue
autofluorescence intensity between the two wavelengths
must not be the same as otherwise normalization of an
image could not be achieved.

15   In the apparatus and method of the present
invention, two wavelengths of light for imaging a tissue
site can be used. Preferably, blue light is used as
excitation light to induce tissue autofluorescence and
red/near-infrared light (approx. 700 nm) is used to
20   produce a remittance light image. Alternatively, a
single wavelength of light can be used as excitation
light and a remittance light image can be collected from
the remitted excitation light. The integrated
autofluorescence image and the remittance light image are
25   combined and displayed in a form to allow the observer to
intuitively adjust for the excitation light intensity
variations.

Accordingly, in a first embodiment, the present
invention provides apparatus for imaging diseases in
30   tissue comprising:

a light source for producing excitation light to
excite the tissue to generate autofluorescence light and
for producing illumination light to generate remittance
light from the tissue;

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optical means for receiving the autofluorescence
light and the remittance light to collect an
autofluorescence light image and a remittance light
image;

5   means for integrating the autofluorescence image
over a range of wavelengths in which the autofluorescence
intensity for normal tissue is substantially different
from the autofluorescence intensity for diseased tissue
to establish an integrated autofluorescence image of the
10   tissue; and

display means for displaying the integrated
autofluorescence image and the remittance light image to
produce a normalized image in which diseased tissue is
distinguishable from normal tissue.

15   In a further aspect the present invention provides,
a method for imaging diseases in tissue comprising:

exciting the tissue to autofluoresce with excitation
light to generate autofluorescence light;

illuminating the tissue with illumination light to
20   generate remittance light;

detecting the autofluorescence light;

integrating the intensity of autofluorescence light
over a range of wavelengths in which the autofluorescence
intensity for normal tissue is substantially different
25   from the autofluorescence intensity for diseased tissue
to establish an integrated autofluorescence image of the
tissue;

detecting the remittance light to establish a
remittance light image; and

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combining the integrated autofluorescence image and
the remittance light image to produce a normalized image
in which diseased tissue is distinguishable from normal
tissue.

5   In a further embodiment, the present invention
provides a fluorescence endoscope apparatus having an
image sensing device that is positioned at the end of a
probe comprised of light guides. The probe is introduced
into the body thereby eliminating the problem of
10   fluorescence image degradation due to light loss while
travelling through the collecting light guides. The
image sensing device can be positioned adjacent to the
tissue surface being examined so that there is little
loss of light.

15   To solve the problem of reliable and accurate
acquisition of a faint fluorescence image the apparatus
of the present invention employs an image sensing device
such as a CCD (or equivalent such as CID) array having a
sensitivity that can be varied. A preferred way to
20   achieve increased sensitivity of the CCD array is to
combine individual pixel sensing elements to create
larger to very large sensing units. Individual sensing
elements can be combined together into 2x2, 4x4, 8x8,
16x16 or even larger groups creating new larger sensing
25   units, particularly if CCDs are used with 100% fill
factor and high quantum efficiency. With special noise
suppressing circuitry very sensitive detectors can be
made with very low noise, i.e. very high signal-to-noise
ratio (SNR), well within parameters to detect the low
30   fluorescence emitted by tissues.

Accordingly, in the further embodiment the present
invention provides an endoscope apparatus for imaging a
disease site within a body comprising:

a probe having an inner end to be located within the
body near the disease site and an outer end to extend
outside the body;

5   a light source at the outer end of the probe for
generating light that includes excitation light to induce
tissue fluorescence, the probe conveying the excitation
light from the outer end to the inner end to illuminate
the disease site and cause the tissue to fluoresce;

image sensing means at the inner end of the probe to
10   detect tissue fluorescence, the image sensing means
having a light sensitivity that can be increased to
acquire low resolution images at low fluorescent light
intensities and decreased to acquire high resolution
images at other light intensities;

15   filtering means at the inner end of the probe for
filtering out the excitation light; and

display means connected to the outer end of the
probe for displaying the filtered image detected by the
image sensing means in such a manner as to delineate
20   diseased and normal tissue due to diseased tissue having
diminished fluorescence in comparison to normal tissue.

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BRIEF DESCRIPTION OF THE DRAWINGS

Aspects of the present invention are illustrated, merely by way of example, in the accompanying drawings in which:

5   Figure 1a is a graph showing a typical autofluorescence curve of light intensity over a range of wavelengths for in vivo tissue exposed to excitation light;

Figures 1b to 1d are graphs showing actual
10   autofluorescence curves for tissue samples;

Figure 2 is a schematic view of a first embodiment of the present invention that employs integrated autofluorescence in which images are acquired simultaneously;

15   Figure 3 is a schematic view of a second embodiment of the present invention in which images are acquired sequentially;

Figure 4 is a schematic view of a third embodiment of the present invention that uses blue light to produce
20   both the autofluorescence and remittance light images; and

Figure 5 is a schematic view of a fourth embodiment of the apparatus of the present invention that employs an CCD array positioned at the tip of an endoscopic probe.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Figure 1a shows a typical graph of the
autofluorescence response spectrum of tissue in vivo when
exposed to blue excitation light (400nm - 450nm).
5 Applicant has discovered that autofluorescence of
diseased tissue in vivo is greatly reduced as compared to
normal tissue through the entire range of visible light
(from approximately 500nm to approximately 700nm).
Figures 1b-1d are examples of actual autofluorescence
10 curves for tissue illuminated by blue excitation light.
In Figure 1b, the autofluorescence spectrum for bronchial
tissue is shown. Note that the autofluorescence
intensity for normal tissue and tumorous tissue both peak
in the green range of the spectrum (approximately 530nm),
15 however, the peak for tumorous tissue is much lower than
the peak for normal tissue. In the region of the
spectrum greater than 700nm, the spectrums for normal and
tumor tissue are substantially identical. Figure 1c
shows the autofluorescence spectrum for larynx tissue
20 that is induced to fluoresce using blue laser light.
Again, there is a pronounced peak in the green region of
the spectrum for normal tissue and a greatly reduced
spectrum for tumor tissue having a low peak in the green
region. In the region of the spectrum greater than 700
25 nm, the spectrum is substantially the same for both
tissues. In Figure 1d, the autofluorescence spectrum for
nasopharynx tissue is shown having a green region peak
for normal tissue and a reduced overall spectrum for
diseased tissue. While there are some differences in the
30 autofluorescence spectrum for specific types of tissue,
in general, the diseased tissue autofluorescence is
significantly reduced in comparison to the normal tissue
autofluorescence over a broad spectral band.

Figure 2 is a schematic view of apparatus according
35 to a first embodiment that has been developed to exploit

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the autofluorescence response of the tissue to
differentiate between diseased and normal tissue.
The apparatus of Figure 2 employs simultaneous
illumination of the tissue with both excitation and

5   illumination light. The apparatus includes a light
source 30 for producing excitation light of a first pre-
selected wavelength, preferably blue light (400-450nm),
to excite the tissue to autofluoresce. The excited
tissue produces a predominantly green autofluorescence

10 light as indicated in Figures 1a-1d. Light source 30
also produces non-excitation light of a different
wavelength to illuminate the tissue. The non-excitation
light is preferably far red to infrared light (λ_R)
including wavelengths greater than 700nm and is used to

15 produced a remittance light image of the tissue. This
non-excitation light is preferred as it falls outside the
relatively broad spectral range of generally green
emitted autofluorescence light ($\Delta\lambda_f$) in which
autofluorescence intensity for normal tissue is

20 substantially greater than for diseased tissue so as not
to interfere with detection of the relatively faint
autofluorescence image. Also, far red to infrared light
has a low absorption coefficient in most tissue and it
has a large scattering coefficient. Additionally, the

25 scattering and absorption coefficients of red to infrared
light do not vary much from location to location in most
tissues so that red and infrared light is almost
uniformly back scattered and reflected from the tissue.
This remittance light is therefore relatively uniform in

30 its angular distribution from the tissue and the
intensity of light will depend almost entirely on the
illumination intensity. Areas that receive less light
will backscatter proportionally less in the same manner
that autofluorescence emits light proportional to the

35 amount of excitation light. Therefore, red and infrared
light can be used to generate an image to correct for
non-uniformity in the autofluorescence image that might

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arise due to changes in the proximity of the excitation
light to the tissue, the angle of incidence of the
excitation light to the tissue and the intensity of the
excitation light. It should be noted that the intensity
5   of remittance light (λ_R) is much greater than the
intensity of the autofluorescence light and a vertical
break in the range over which remittance light is
collected is provided in Figure 1a to account for this
intensity difference.

10   The light is delivered to the tissue under
examination by a conventional endoscope probe 32
comprising a bundle of optical fibres. Probe 32 also
delivers autofluorescence light and remittance light from
the tissue to optical means in the form of CCD cameras 34
15   and 36. CCD camera 36 has associated means for
integrating the intensity of the autofluorescence light
over a range of wavelengths in which the autofluorescence
intensity for normal tissue is substantially different
from the autofluorescence intensity for diseased tissue
20   to establish an integrated autofluorescence intensity
image of the tissue. The means for integrating the
intensity of autofluorescence light preferably comprises
a broad band filter 49 to admit autofluorescence light
over a broad range of wavelengths. In the case of blue
25   excitation light, the resulting autofluorescence tends to
be mainly green light and the intensity is integrated
over the range of wavelengths from 500-650nm designated
$(\Delta\lambda_f)$ in Figure 1. In this manner, the need for an image
intensifier is obviated as the integrated
30   autofluorescence signal is nearly an order of magnitude
stronger compared to the natural autofluorescence
intensity in a narrow wave band. In addition, the
detected change (DC) between normal and abnormal tissue
is approximately 8-10 times, compared to the 1.5 - 2
35   times of prior art systems.

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Referring to Figure 1, the DC is defined as:

$$DC_{application} = \frac{N}{D}$$

$$DC_{priorart} = \frac{\frac{N}{D}}{\frac{n}{d}}$$

where

N = the autofluorescence intensity for normal tissue at
    a wavelength exhibiting the maximum difference
5   between normal and diseased tissue
D = the autofluorescence intensity for diseased tissue
    at a wavelength exhibiting the maximum difference
    between normal and diseased tissue
n = the autofluorescence intensity for normal tissue at
10   a wavelength exhibiting the minimum difference
    between normal and diseased tissue
d = the autofluorescence intensity for diseased tissue
    at a wavelength exhibiting the minimum difference
    between normal and diseased tissue

15   Since n/d is usually greater than 1 (in the range of
2 to 5) in prior art systems, the detected change for the
apparatus and method of the present invention is
generally 2 to 5 times greater than the detected change
of the prior art.

20   The images captured by CCD cameras 34 and 36 are
processed and displayed on display means in the form of a
monitor 40. The images are preferably processed in an
imaging board in a computer. The integrated
autofluorescence image captured by camera 36 and the
25   remittance light image captured by camera 34 are combined
to produce a normalized image in which diseased tissue is
distinguishable from normal tissue. Camera 36 provides a
substantially green integrated autofluorescence image
that is fed to the green channel of the display and
30   camera 34 provides a substantially red remittance light

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image to normalize the autofluorescence image that is fed
to the red channel of the display to produce a normalized
pseudo-colour image. If diseased tissue is present, the
intensity of the green autofluorescence image will be
5   reduced over the diseased area while the remittance light
image will be substantially unaffected. If tissue is
normal, the intensity of the green autofluorescence image
will be increased relative to the diseased tissue and the
remittance light image will continue to be substantially
10 unaffected. Combining and display of the two images on
monitor 40 is arranged such that the relatively constant
red remittance light image is used to establish a
"underlying" image that accurately displays contours in
the tissue and image variations that arise due to the
15 proximity and intensity of the light source to the
tissue. The mix of the images is such that normal tissue
will appear green and diseased tissue will appear red due
to the reduced levels of green autofluorescence in the
vicinity of the diseased tissue allowing the red
20 remittance light to predominate.

The apparatus of Figure 2 is set up such that light
source 30 illuminates tissue 42 with the excitation light
and illumination light simultaneously and separate CCD
cameras 34 and 36 are provided to receive the
25 autofluorescence image and the remittance light image.
In this arrangement, light splitting means in the form of
dichroic mirrors 44 and 46 are provided to direct the
remittance light and the autofluorescence light to the
appropriate CCD camera. While traditional 50%, 50% or
30 X%, 100-X% beam splitters may be used, dichroics increase
the fluorescence image intensity available to be
detected. In Figure 2, a first dichroic mirror 44 passes
the red remittance light (R) to CCD camera 34 and diverts
the green autofluorescence light (G) and reflected blue
35 excitation light (B) to second dichroic mirror 46.
Second dichroic mirror 46 diverts the green

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autofluorescence light (G) to CCD camera 36 and passes
the blue excitation light (B).

Filter 49 in the path of the autofluorescence light
is preferably adjustable to vary the range of wavelengths
5   of autofluorescence light that are received by CCD camera
36. In this manner, the "window" over which
autofluorescence is integrated can be varied to fine tune
the apparatus to detect different disease conditions in
different tissues that tend to exhibit characteristic
10   autofluorescence spectra as illustrated in Figures 1b to
1d. Filter 49 can be varied by inserting an appropriate
filter into place for the particular tissue and the type
of tumour under examination.

In addition, an optional filter means 50 can be
15   included in the light path to prevent blue excitation
light from being received by the CCD cameras.

While the apparatus of Figure 2 employs simultaneous
illumination of the tissue with both excitation and
illumination light, it is also possible to expose the
20. tissue to excitation light and illumination light
sequentially. Figure 3 schematically illustrates imaging
apparatus according to a second embodiment of the present
invention that illuminates the tissue sequentially over a
timing cycle. Light source 30 illuminates tissue 42
25   through endoscope 32 with excitation light for a first
portion of the timing cycle. Autofluorescence light is
delivered via endoscope 32 and filter 60 to a single CCD
camera 62 in order to capture an integrated
autofluorescence image. Filter 60 is positionable before
30   camera 62 to filter out the excitation light and pass
broadband autofluorescence light. The captured
autofluorescence image is transferred to image processing
means and then to image storage means located in a
computer 63. Light source 30 then illuminates the tissue

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with illumination light to generate a remittance light
image. If necessary, filter 65 is moved into position to
filter the remittance light. Filters 60 and 65 are
mounted on a turntable arrangement 67 that is controlled
5   by computer 63. The remittance light image is
transferred to the image processing and storage means.
The two images collected in the timing cycle are then
combined and displayed on monitor 40 in the same manner
as previously described using colour to delineate normal
10   and diseased tissue. The cycle is then repeated under
the control of computer 63.

     The foregoing embodiments of the present invention
employ blue excitation light and red illumination light
to produce an image that distinguishes normal and
15   diseased tissue. In certain conditions, such as when
examining inflamed tissue, the foregoing systems may
cause false positive readings. In order to reduce false
positive readings for cancer, a third embodiment of the
present invention has been developed that employs blue
20   light as both the excitation light and the illumination
light. Figure 3 is a schematic drawing of the apparatus
of the third embodiment that is designed to reduce the
rate of false positive readings without sacrificing true
diseased tissue (true positive) detection rates.

25   False positive readings arise in inflamed tissue as
the increased blood concentration tends to absorb blue
excitation light and green autofluorescence light leading
to a reduced autofluorescence signal. For prior art
autofluorescence systems, the blood absorption causes a
30   large drop in the green autofluorescence image and a
slightly less large drop in the red autofluorescence
image causing the displayed image to show inflamed tissue
differently from normal tissue leading to mistaken
identification as diseased tissue. For the blue
35   excitation light, red illumination light imaging of the

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present invention, the same problems occur. The
integrated fluorescence drops and the red remittance
image does not change significantly in areas of inflamed
tissue, consequently, the displayed image does not appear
5   to show normal tissue and the inflamed area is mistaken
for diseased tissue.

In the apparatus of Figure 3, light source 30
provides blue light for both excitation and illumination
light in a manner identical to the embodiment of Figure
10   2. Green autofluorescence light (G) and blue remittance
light (B) are collected from the tissue site. The
combined light is split at dichroic mirror 44. A blue
remittance light image is captured by CCD camera 34 and a
green autofluorescence image is reflected through
15   integrating filter 49 for capture by CCD camera 49. In
this arrangement, the intensity of the detected blue
remittance light image tends to drop off almost as much
as the green integrated fluorescence image, consequently,
the displayed image of inflamed tissue does not differ
20   significantly from normal tissue.

An additional modification of the apparatus of the
third embodiment can be used to make the presence of
increased blood at a tissue site appear as a recognizable
colour on the displayed image that would not be confused
25   with normal or diseased tissue. In the modified
apparatus, blue excitation light and red illumination
light are used and a blue remittance light image, a red
remittance light image and a green integrated
autofluorescence image are collected. The red and blue
30   remittance images are captured by camera 34. Camera 34
sends the red remittance image via its red channel and
the blue remittance image via its blue channel to display
40. The green integrated autofluorescence image is
captured by camera 36 and sent to the green channel of
35   the display. On the display, normal tissue appears

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white, inflamed tissue has a reddish hue and abnormal
tissue has a purplish hue.

The technique of the present invention also allows
development of an imaging system that is sufficiently
5 small and compact to be positioned at the end of an
endoscope probe. Referring to Figure 5, there is shown
an endoscope system 2 for imaging a disease site within a
body according to a fourth embodiment of the present
invention. The apparatus includes a probe 4 having an
10 inner end 6 that is insertable into a body to be located
near the disease site. The outer end of probe 4 remains
outside the body for connection to a light source 8 for
generating light and display means in the form of a
colour monitor 10 for displaying the image collected by
15 probe 4.

Light source 8 generates light at the outer end of
the probe that includes excitation light to induce tissue
fluorescence. The probe is comprised of a bundle of
optical fibres 10 that convey the light of source 8 from
20 the outer end to inner end 6 to illuminate the disease
site. At inner end 6, there is provided image sensing
means, preferably in the form of CCD sensor 12 to detect
and collect an image of the diseased site using
remittance light and emitted fluorescent light. CCD
25 array 12 communicates with the outer end of probe 4 via
electrical connection 14 that extends through probe 4.

Preferably, inner end 6 is provided with a lens 15
to focus light on CCD sensor 12. Filtering means in the
form of a filter module 16 is positioned before CCD
30 sensor 12. Filter module 16 can be fixed in place or
removable remotely. Alternatively, the filtering means
can be a coating applied directly to surface of CCD
sensor 12. In a still further arrangement, filter module
16 can be associated with lens 15. The filter module 16

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acts to exclude excitation light and pass light of other
wavelengths to the image sensing means, particularly
emitted fluorescent light.

5   The image collected by CCD sensor 12 is transmitted
via line 14 to the outer end of probe 4 for viewing on
display means in the form of a colour monitor 18. The
image displayed on monitor 18 delineates diseased and
normal tissue for viewing by the endoscope operator.

10   The endoscope apparatus of the fourth embodiment is
able to collect the faint fluorescence images that
provide information necessary for delineating diseased an
normal tissue by virtue of the fact that CCD sensor 12
is provided with a light sensitivity that can be
increased to acquire low resolution images at low
15   fluorescent light intensities and decreased to acquire
high resolution images at other light intensities.

        The light sensitivity of CCD sensor 12 is adjusted
by binning the pixels of the sensor array. Binning the
pixels decreases spatial resolution. For example, a CCD
20   sensor comprised of 250x250, (i.e. 62,500 active pixels)
if binned to form 8x8 pixels per each new sensor unit
would yield an effective CCD of approximately 30x30
pixels (each pixel being 64 times larger than the
original pixels) providing a very low resolution image.
25   However, dynamic binning can solve the problem of the low
spatial resolution as will be described below.

        In operation, light source 8 can provide a broad
spectral band of excitation light ranging in wavelength
between 400-480nm (broad band blue light). Such an
30   excitation light tends to generate a strong fluorescence
response in most tissues such as the lungs, the
esophagus, the colon, the bladder and the skin. The peak
fluorescence is in the green region at approximately

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510nm and it has been shown that the fluorescence signal
is greatly diminished or virtually disappears in abnormal
tissue due to early cancer or dysplasia. Alternatively,
the excitation light can be in a narrow spectral band of
5   blue or violet light.

    The blue excitation light of light source 8 is
conveyed to inner probe end 6 to illuminate an internal
disease site to induce maximum tissue fluorescence
particularly in the green and longer wavelengths.
10 Scattered/reflected excitation light and fluorescence
light are focused by lens 15 on CCD sensor through filter
module 16. Filter module 16 is selected to filter out
the blue band excitation light such that only the
fluorescence green and longer wavelengths (e.g. greater
15 than 480nm) are collected by the CCD sensor. Since
abnormal tissue has greatly diminished (or a lack of)
fluorescence particulary in the green region, the
abnormal tissue will be detected as a darker area on the
image captured by the CCD sensor. The darker abnormal
20 regions of tissue will be readily apparent on display
monitor 18. The light sensitivity of the CCD sensor can
be increased by binning to acquire low resolution images
at low fluorescent light intensities. While the images
are of reduced resolution, they are generally
25 sufficiently detailed to accurately determine the extent
and location of the diseased tissue.

    The arrangement of the fourth embodiment of the
present invention reduces the complexity of the apparatus
as there is generally no longer the need for an image
30 intensifier to enhance the image collected by the CCD
sensor since the sensor is located immediately adjacent
the image site and the binning of the CCD sensor permits
acquisition of very faint fluorescence images albeit at
reduced resolution.

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    In a variation of the fourth embodiment, high resolution non-fluorescence images and low resolution fluorescence images of the disease site can be acquired sequentially and combined for display on monitor 18. In

5   this variation, the endoscope apparatus is identical to the fourth embodiment except light source 8 is modified to sequentially illuminate the disease site with two or more wavelengths of light over a timing cycle. One wavelength is a fluorescence excitation light that is on

10 for the majority of the timing cycle and the other wavelength is a non-excitation light that is on for a short period of the timing cycle. This arrangement requires means to increase the image sensing means sensitivity to acquire a low resolution fluorescence

15 image during illumination by the fluorescence excitation light and decrease the image sensing means sensitivity to acquire a high resolution image during illumination by the non-excitation light. This arrangement also requires image processing means for storing sequential images

20 captured by the image sensing means and combining the images for display as a pseudo-colour image on the display means.

    Preferably, the endoscope apparatus of the present embodiment is operated in the following manner:

25   Light source 8 sequentially illuminates the disease site briefly through probe 6 with red non-excitation light and blue fluorescence excitation light over a single cycle of 30msec which is consistent with video display rates. The scattered and/or reflected red light

30 is passed through filter module 16 in front of the CCD sensor 12. The red light is sufficiently intense that CCD sensor 12 does not have to be binned and an image of the site at high resolution is captured by the sensor. The illumination with red light is of short duration

35 (e.g. 5msec pulse) and the image is stored in a buffer of

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the image processing means comprising an imaging board
20. The blue light is of much longer duration (e.g.25
msec) to collect sufficient fluorescence light generated
by the blue light. In addition, the CCD is now binned if
5   necessary to detect and capture the fluorescence image of
the site at reduced resolution. Filter module 16
excludes the blue excitation light and permits passage of
green and longer wavelengths. The captured fluorescence
image is fed into another buffer of the imaging board. A
10   pseudo image is then formed by the imaging board for
display on RGB monitor 18. The pseudo image is a
composite image that includes a very high resolution
colour image (generated using the red light) superimposed
on a green to dark green lower resolution image
15   (generated using the blue light). In the composite
image, normal tissue will be green and diseased or
abnormal tissue will show up as red or pink areas. This
combination of fluorescence and reflectance imaging has
the additional advantage of compensating for changes in
20   fluorescence intensity due to variation in the distance
and angle between the probe and the surface of the body
cavity.

Although the present invention has been described in
some detail by way of example for purposes of clarity and
25   understanding, it will be apparent that certain changes
and modifications may be practised within the scope of
the appended claims.

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WE claim:

     1.   Apparatus for imaging diseases in tissue comprising:

     a light source for producing excitation light to
5 excite the tissue to generate autofluorescence light and for producing illumination light to generate remittance light from the tissue;

     optical means for receiving the autofluorescence light and the remittance light to collect an
10 autofluorescence light image and a remittance light image;

     means for integrating the autofluorescence image over a range of wavelengths in which the autofluorescence intensity for normal tissue is substantially different
15 from the autofluorescence intensity for diseased tissue to establish an integrated autofluorescence image of the tissue; and

     display means for displaying the integrated autofluorescence image and the remittance light image to
20 produce a normalized image in which diseased tissue is distinguishable from normal tissue.

     2.   Apparatus as claimed in claim 1 in which the excitation light is blue light including wavelengths in the range of 400nm - 450nm.

25   3.   Apparatus as claimed in claim 1 in which illumination light is red to near infrared light including wavelengths greater than 700nm.

     4.   Apparatus as claimed in claim 1 in which the illumination light is the same as the excitation light.

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5. Apparatus as claimed in claim 1 in which the autofluorescence intensity is integrated over the range of wavelengths from 500-700nm.

6. Apparatus as claimed in claim 1 in which the
5   light source illuminates the tissue with the excitation light and illumination light simultaneously.

7. Apparatus as claimed in claim 6 in which the optical means comprises a pair of CCD cameras, one camera receiving the autofluorescence image and the other camera
10   receiving the remittance light image.

8. Apparatus as claimed in claim 7 including light splitting means for directing the remittance light to one CCD camera and the autofluorescence light to the other camera.

15   9. Apparatus as claimed in claim 8 in which the light splitting means comprise a first dichroic mirror to divert the remittance light to one CCD camera and pass the autofluorescence light and excitation light to a second dichroic mirror, the second dichroic mirror
20   diverting the autofluorescence light to the other CCD camera and passing the excitation light.

10. Apparatus as claimed in claim 1 in which the means for integrating the autofluorescence image comprise an adjustable filter to vary the wavelengths of
25   autofluorescence light that are received by the optical means.

11. Apparatus as claimed in claim 1 including filter means for preventing excitation light from being received by the optical means.

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12.   Apparatus as claimed in claim 1 in which the
light source illuminates the tissue with excitation light
and illumination light sequentially over a timing cycle.

13.   Apparatus as claimed in claim 12 including
5   image storage means for storing sequential images
captured by the optical means, the stored sequential
images being combined and displayed on the display means.

14.   Apparatus as claimed in claim 1 in which the
display means comprises a colour monitor having green and
10   red signal channels, the integrated autofluorescence
image being fed to the green channel of the monitor and
the remittance light image being fed to the red channel
to produce a normalized pseudo-colour image in which
diseased tissue appears red and normal tissue appears
15   green.

15.   Apparatus as claimed in claim 4 in which the
display means comprises a colour monitor having green and
blue signal channels, the integrated autofluorescence
image being fed to the green channel of the monitor and
20   the remittance light image being fed to the red channel
to produce a normalized pseudo-colour image in which
diseased tissue appears blue and normal tissue appears
green.

16.   Apparatus as claimed in claim 1 including
25   optical means for receiving reflected excitation light to
collect an excitation light image.

17.   Apparatus as claimed in claim 16 in which the
display means comprises a colour monitor having red,
green and blue signal channels, the integrated
30   autofluorescence image being fed to the green channel of
the monitor, the remittance light image being fed to the
red channel and the excitation light image being fed to

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the blue channel to produce a normalized pseudo-colour
image in which normal tissue appears white, inflamed
tissue has a reddish hue and diseased tissue has a
purplish hue.

5   18. Apparatus as claimed in claim 1 including an
optical probe having an inner end for insertion within a
body and an outer end to extend outside the body for
transmitting light to and from the tissue under
examination.

10   19. Apparatus as claimed in claim 18 in which the
optical means is positioned proximal the inner end of the
optical probe.

          20. Apparatus as claimed in claim 19 in which the
optical means comprise a CCD array.

15   21. A method for imaging diseases in tissue
comprising:

          exciting the tissue to autofluoresce with excitation
light to generate autofluorescence light;

          illuminating the tissue with illumination light to
20 generate remittance light;

          detecting the autofluorescence light;

          integrating the intensity of autofluorescence light
over a range of wavelengths in which the autofluorescence
intensity for normal tissue is substantially different
25 from the autofluorescence intensity for diseased tissue
to establish an integrated autofluorescence image of the
tissue;

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detecting the remittance light to establish a remittance light image; and

combining the integrated autofluorescence image and the remittance light image to produce a normalized image
5   in which diseased tissue is distinguishable from normal tissue.

22.   A method as claimed in claim 21 in which the excitation light is blue light (400nm - 450nm)

23.   A method as claimed in claim 21 in which the
10   illumination light is far red to infrared light including wavelengths greater than 700nm.

24.   A method as claimed in claim 21 in which the illumination light is the same as the excitation light.

25.   A method as claimed in claim 21 in which the
15   autofluorescence intensity is integrated over the range of wavelengths from 500-700nm.

26.   A method as claimed in claim 21 in which the steps of exciting the tissue and illuminating the tissue with illumination light are carried out simultaneously.

20   27.   A method as claimed in claim 21 in which the steps of exciting the tissue and illuminating the tissue with illumination light are carried out sequentially.

28.   A method as claimed in claim 21 in which the remittance light image is detected at wavelengths in
25   which the autofluorescence intensity for normal tissue is substantially similar to the autofluorescence intensity for diseased tissue to establish a remittance light image of the tissue.

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29. Endoscope apparatus for imaging a disease site within a body comprising:

a probe having an inner end to be located within the body near the disease site and an outer end to extend
5   outside the body;

a light source at the outer end of the probe for generating light that includes excitation light to induce tissue fluorescence, the probe conveying the excitation light from the outer end to the inner end to illuminate
10   the disease site and cause the tissue to fluoresce;

image sensing means at the inner end of the probe to detect tissue fluorescence, the image sensing means having a light sensitivity that can be increased to acquire low resolution images at low fluorescent light
15   intensities and decreased to acquire high resolution images at other light intensities;

filtering means at the inner end of the probe for filtering out the excitation light; and

display means connected to the outer end of the
20   probe for displaying the filtered image detected by the image sensing means in such a manner as to delineate diseased and normal tissue due to diseased tissue having diminished fluorescence in comparison to normal tissue.

30.   Endoscope apparatus as claimed in claim 29 in
25   which the image sensing means is a CCD.

31.   Endoscope apparatus as claimed in claim 23 in which the light sensitivity of the image sensing means is increased by binning pixels of the CCD array.

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32. Endoscope apparatus as claimed in claim 30 in which the filtering means comprises a coating on the CCD array.

33. Endoscope apparatus as claimed in claim 29 including a lens at the inner end of the probe to focus fluorescence light on the image sensing means.

34. Endoscope apparatus as claimed in claim 29 in which the light source generates excitation light in a broad spectral band ranging from 400nm to 480nm.

35. Endoscope apparatus as claimed in claim 29 in which the light source generates excitation light in a narrow spectral band of blue or violet light.

36. Endoscope apparatus as claimed in claim 29 in which the filtering means comprises a long pass blue filter positioned before the image sensing means.

37. Endoscope apparatus as claimed in claim 29 in which the filtering means excludes excitation light and passes light of other wavelengths to the image sensing means.

38. Endoscope apparatus as claimed in claim 37 in which the filtering means excludes blue excitation light and passes green and longer wavelength light.

39. Endoscope apparatus as claimed in claim 37 in which the light source sequentially illuminates the disease site with two or more wavelengths of light over a timing cycle, one wavelength being an excitation light and the other wavelengths being non-excitation light, and including means to increase the image sensing means sensitivity to acquire a low resolution fluorescence image during illumination by the excitation light and

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decrease the image sensing means sensitivity to acquire a high resolution reflectance image during illumination by the non-excitation light.

40.   Endoscope apparatus as claimed in claim 39 in
5   which the excitation light is on for the majority of the timing cycle and the non-excitation light is on for the remainder of the timing cycle.

41.   Endoscope apparatus as claimed in claim 39 including image processing means for storing sequential
10   images captured by the image sensing means and combining the fluorescence and reflectance images for display as a pseudo-colour image on the display means.

42.   Endoscope apparatus as claimed in claim 39 in which the light source illuminates the disease site with
15   red non-excitation light and blue excitation light.
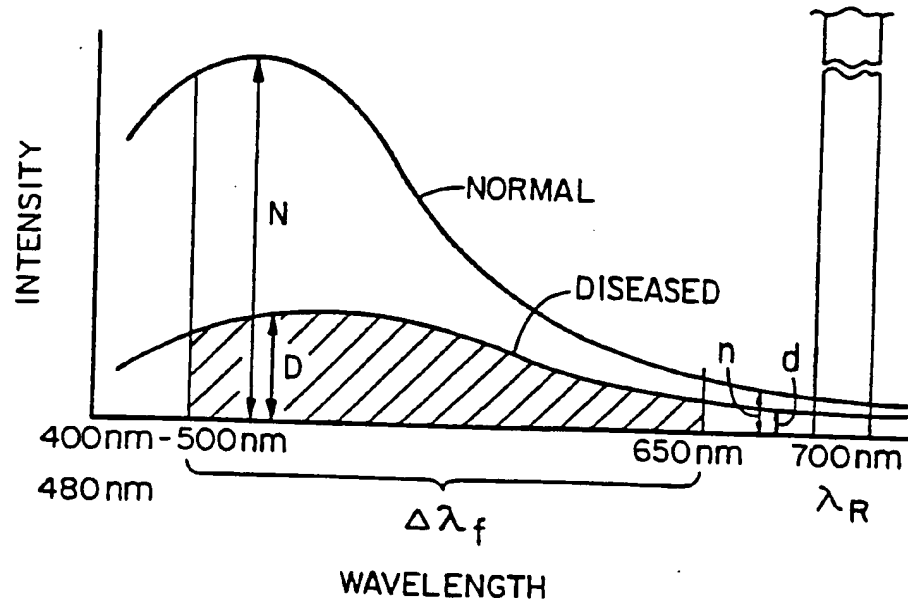
FIG. 1a
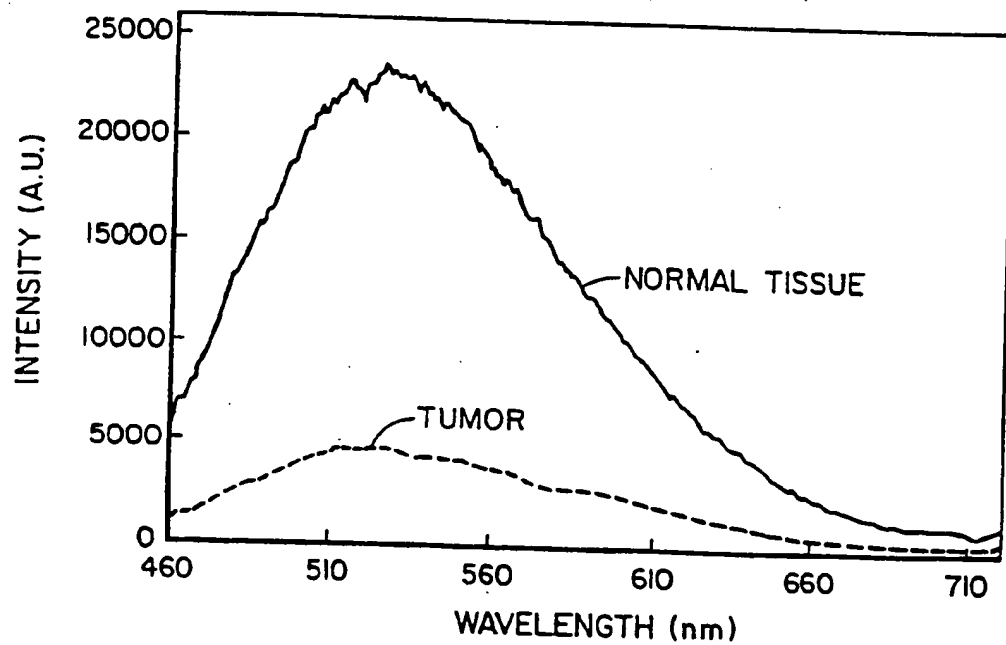
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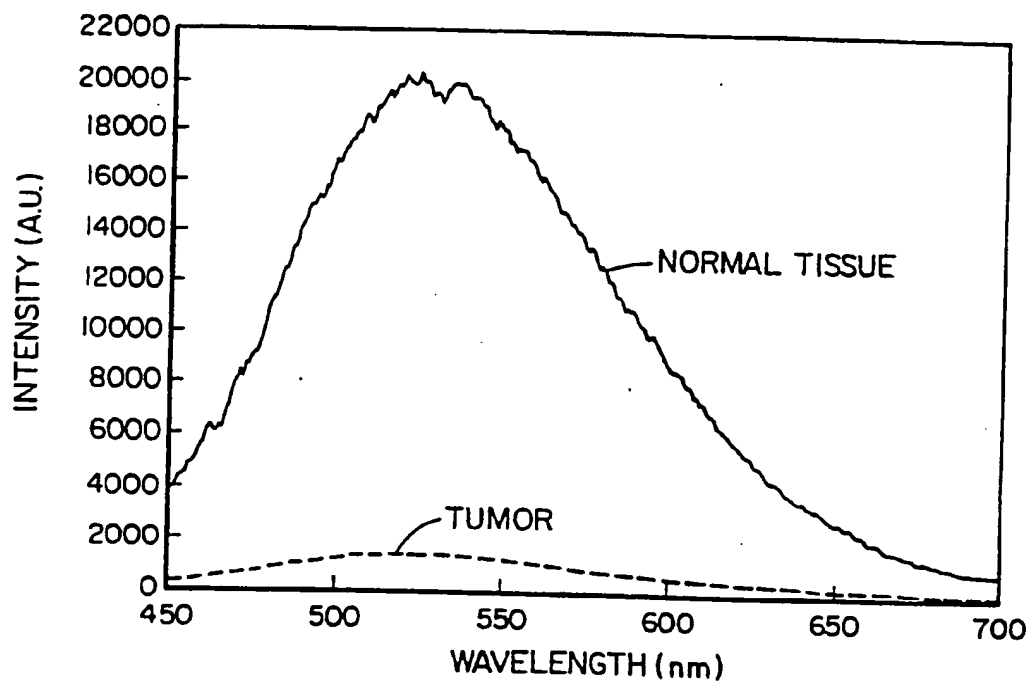
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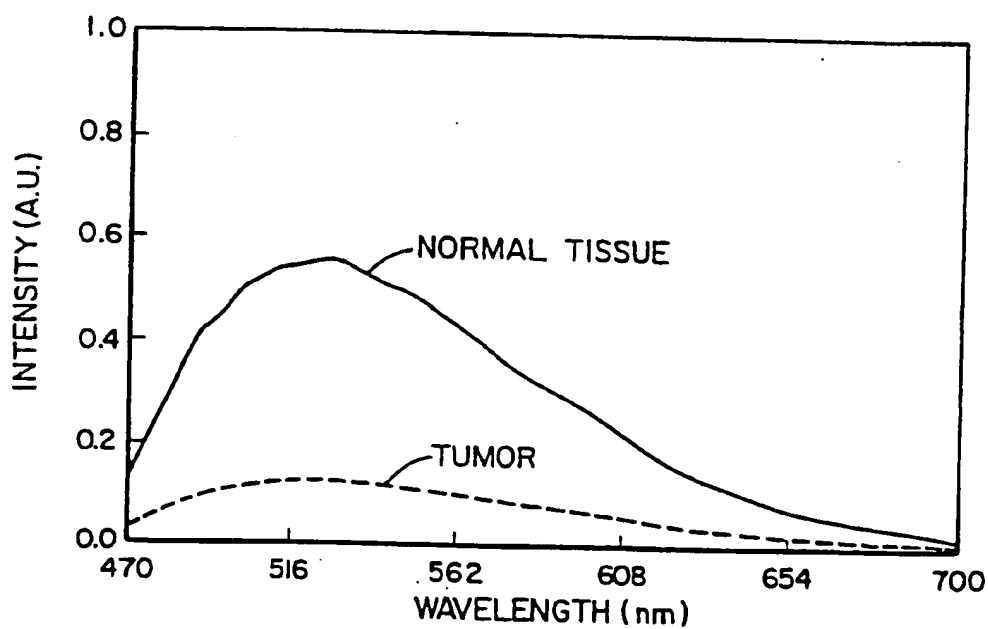
FIG. 1d

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FIG. 2
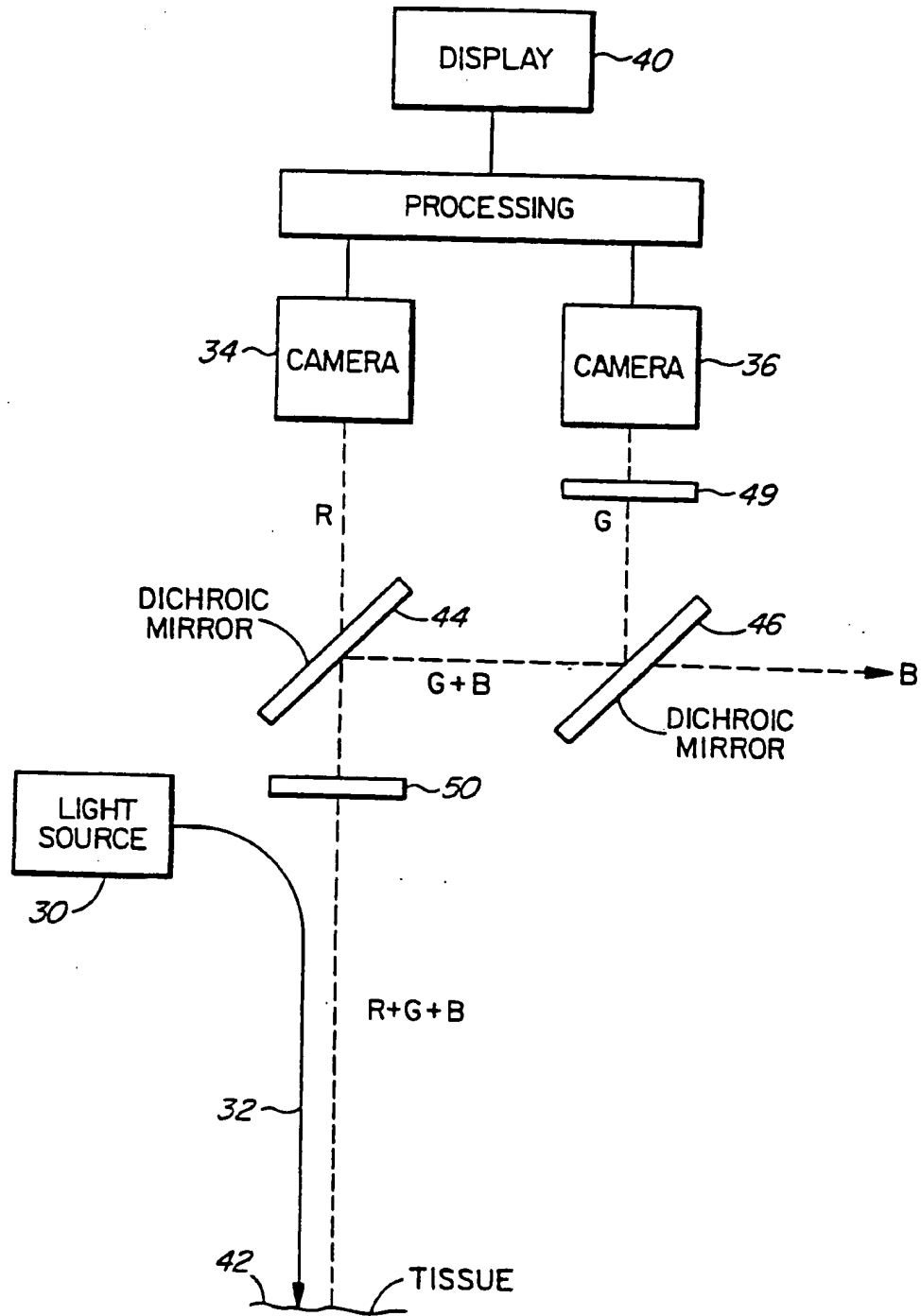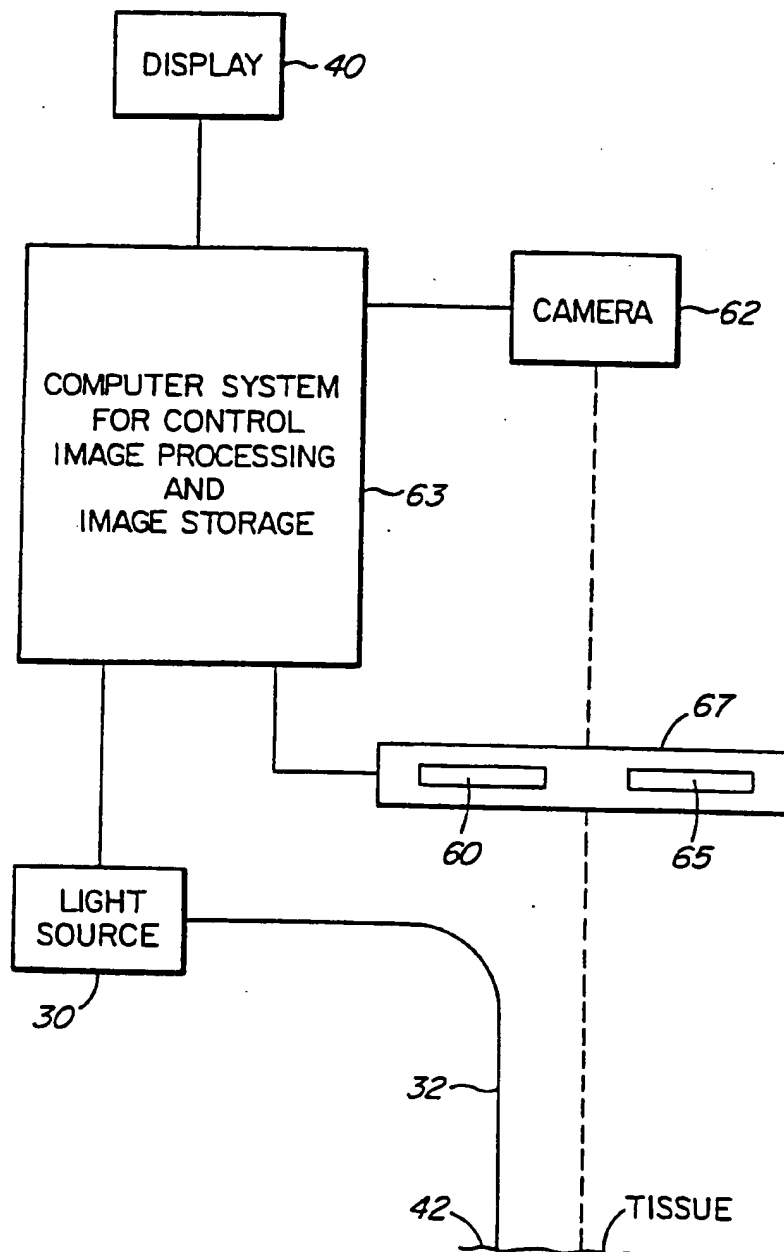
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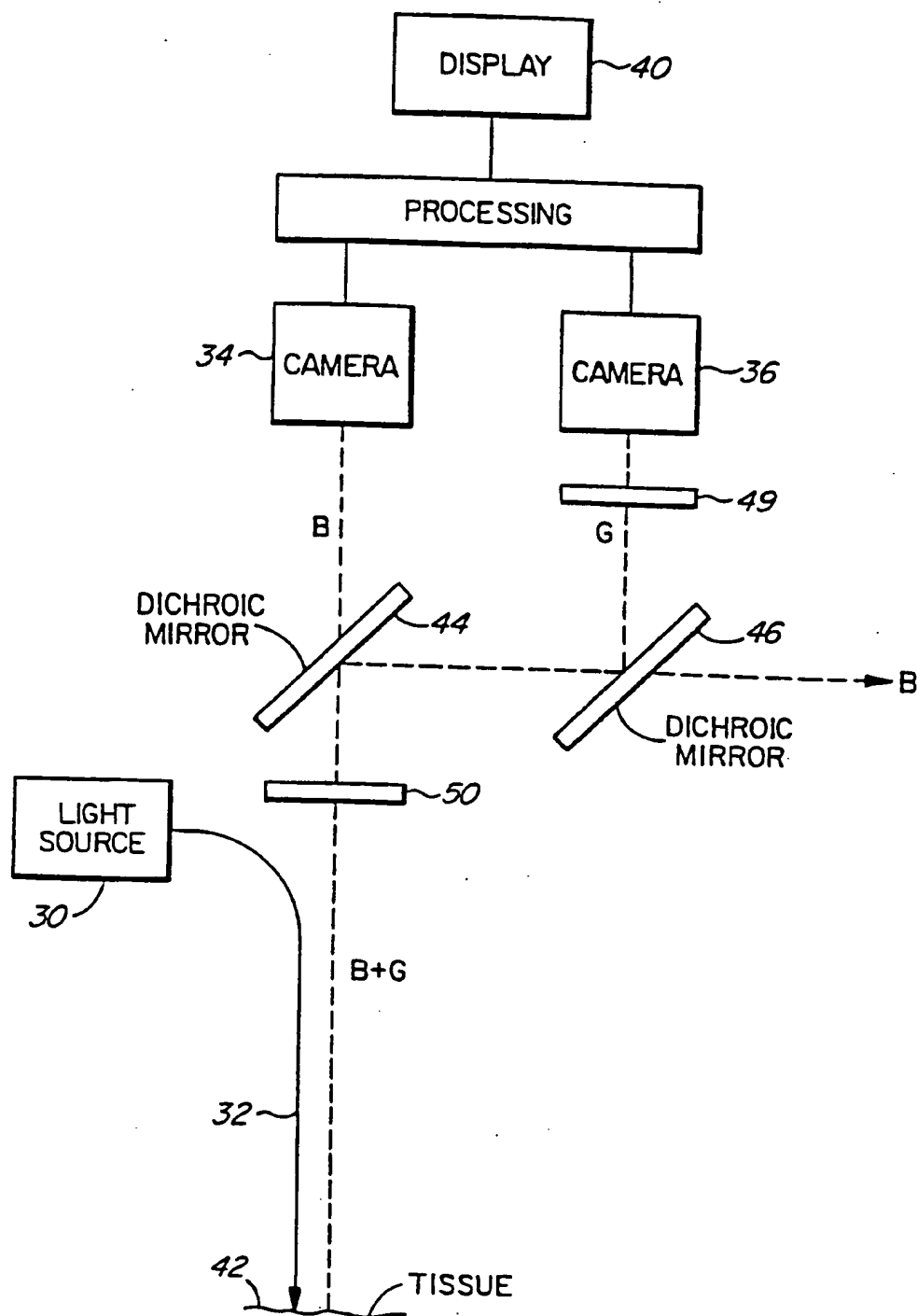
FIG. 3

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FIG. 4

FIG. 5

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